CHAPTER 2

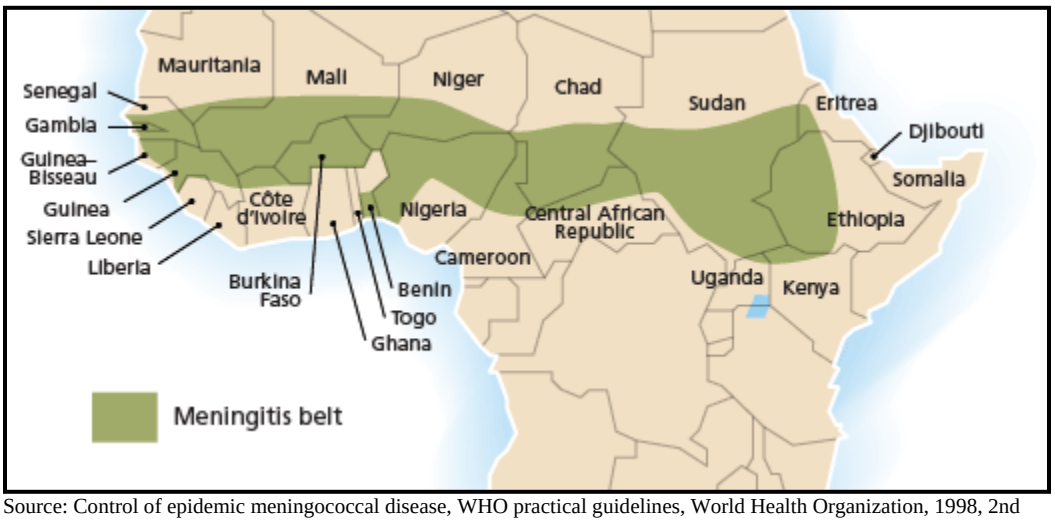
Epidemiology of Meningitis Caused by *Neisseria meningitidis, Streptococcus pneumoniae,* and *Haemophilus influenzae*

The term "meningitis" describes inflammation of the membranes (meninges) and/or cerebrospinal fluid (CSF) that surrounds and protects the brain and spinal cord. Meningitis can result from many causes, both infectious and non-infectious. Bacterial meningitis is a life-threatening condition that requires prompt recognition and treatment. Beyond the newborn period, the most common causes of bacterial meningitis are *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. All three of these organisms are respiratory pathogens. They are spread from person to person by close contact with respiratory secretions. Once acquired, each species can colonize the mucosa of the nasopharynx and oropharynx, which is known as pharyngeal carriage. From there, they may cross the mucosa and enter the blood. Once in the blood, they can reach the meninges, causing meningitis, or other body sites causing other syndromes. Over 1.2 million cases of bacterial meningitis are estimated to occur worldwide each year (24). The incidence and case-fatality rates for bacterial meningitis vary by region, country, pathogen, and age group. Without treatment, the case-fatality rate can be as high as 70 percent, and one in five survivors of bacterial meningitis may be left with permanent sequelae including hearing loss, neurologic disability, or loss of a limb (18).

Neisseria meningitidis

N. meningitidis may either be encapsulated or unencapsulated. However, nearly all invasive *N. meningitidis* organisms are encapsulated, or surrounded by a polysaccharide capsule. This capsular polysaccharide is used to classify *N. meningitidis* into 12 serogroups. Six of these serogroups cause the great majority of infections in people: A, B, C, W135, X, and Y (12). Incidence rates of *N. meningitidis* meningitis are generally highest in children less than five years of age and in adolescents. *N. meningitidis* can also cause a severe bacteremia, called meningococcemia. The worldwide distribution of serogroups of *N. meningitidis* is variable. In the Americas, Europe, and Australia, serogroups B and C are the most common, while serogroup A causes the majority of disease in Africa and Asia (7). Sometimes serogroups can emerge, increasing in importance in a specific country or region, like serogroup C in China (20) or serogroup Y in North America (15, 17, 23).

Worldwide, the incidence of meningitis due to *N. meningitidis* is highest in a region of sub-Saharan African known as the "meningitis belt" (Figure 1). This hyper-endemic region extends from Senegal to Ethiopia, and is characterized by seasonal epidemics during the dry season (incidence rate: 10-100 cases per 100,000 population), punctuated by explosive epidemics in 8-12 year cycles (incidence rates can be greater than 1,000 cases per 100,000 population). Across the meningitis belt, at least 350 million people are at risk for meningitis during these annual epidemics. Meningitis epidemics are generally caused by serogroup A, although outbreaks have also been caused by serogroups C, W135, and X (1-3, 7, 13, 21, 28). Outbreaks of different serogroups may overlap, therefore, laboratory confirmation is important both to recognize and monitor the progression of outbreaks (5-7).



Source: Control of epidemic meningococcal disease, WHO practical guidelines, World Health Organization, 1998, 2nd edition, WHO/EMC/BAC/98.3

Figure 1. The African meningitis belt. These sub-Saharan countries are at high epidemic risk for meningococcal meningitis.

Haemophilus influenzae

H. influenzae, like *N. meningitidis*, may be either unencapsulated or encapsulated with a polysaccharide capsule. The makeup of this polysaccharide capsule allows encapsulated *H. influenzae* isolates to be classified into six serotypes (a, b, c, d, e, and f) with the most common cause of invasive disease being *H. influenzae* type b (Hib). Though *H. influenzae* meningitis is rare in adolescents and adults, rates of meningitis due to Hib are highest in children less than five years of age, with an estimated incidence rate of 31 cases per 100,000 (22). In young children, the case-fatality rate for meningitis due to *H. influenzae* is generally higher than that for meningitis due to *N. meningitidis*. In addition to meningitis, *H. influenzae* is also an important cause of pneumonia as well as epiglottitis. While the worldwide burden of disease caused by *H. influenzae* is not completely understood, lab networks supporting surveillance systems such as Paediatric Bacterial Meningitis (PBM) and Invasive Bacterial Diseases (IBD) contribute standardized disease burden data.

Streptococcus pneumoniae

S. pneumoniae, like *N. meningitidis* and *H. influenzae*, is an encapsulated bacterium. The diversity of capsular types is large, with at least 93 serotypes recognized based on the composition of the capsular polysaccharide. Many *S. pneumoniae* serotypes are capable of causing invasive disease, including meningitis, bloodstream infections, and pneumonia; however, most disease worldwide is caused by a small number of common serotypes (8). The relative contribution of each serotype to the local burden of disease varies globally, with serotypes 1 and 5 more prominent in developing countries. *S. pneumoniae* and Hib disease may vary seasonally, and while they do not cause epidemics like *N. meningitidis*, large outbreaks do occur rarely (4, 12). Meningitis due to *S. pneumoniae* occurs most commonly in the very young and the very old, with an estimated incidence rate of 17 cases per 100,000 population in children

less than five years of age (14). The case fatality rate for meningitis due to *S. pneumoniae* in children less than five years of age exceeds 73% in some parts of the world.

Prevention and control

The risk of secondary cases of meningococcal disease among close contacts of someone with meningococcal disease (i.e., household members, day-care center contacts, or anyone directly exposed to the patient's oral secretions) is high. In non-epidemic settings, antimicrobial chemoprophylaxis is effective in preventing secondary cases among close contacts by eliminating nasopharyngeal carriage if administered rapidly after the index case is identified. Such intervention may not be feasible in many countries. Mass chemoprophylaxis to prevent/control epidemics is not recommended. Secondary cases are also seen for Hib meningitis, particularly in unvaccinated children less than 4 years of age who are exposed to someone with Hib disease. Oral rifampin is recommended to eliminate nasopharyngeal carriage and prevent disease in these children. Secondary meningitis cases are very rare among those exposed to a patient with pneumococcal disease.

Laboratory surveillance data are critical to tracking the spread of less susceptible strains and to providing guidance in the empirical selection of antimicrobial agents. For all three bacterial meningitis pathogens, antimicrobial resistance has been identified, affecting the treatment of patients and chemoprophylaxis of close contacts. *N. meningitidis* isolates resistant to sulfonamides are common in many countries. Isolates resistant to rifampicin, penicillin, chloramphenicol, cotrimoxazole, ceftriaxone, and ciprofloxacin have also been identified (27). One report from the United States described 2 isolates which were rifampin resistant (16). Resistance to beta-lactam antimicrobials is common in *H. influenzae* isolates; the majority of which produce beta-lactamase. *S. pneumoniae* isolates have been reported with resistance to beta-lactams, macrolides, tetracycline, and trimethoprim/sulfamethoxazole. The increasing proportion of pneumococci resistant to penicillin and the development of resistance to ceftriaxone has huge implications for treatment and makes prevention through vaccination that much more important. The introduction of vaccine in the United States has resulted in a decreasing proportion of invasive isolates that are antibiotic-resistant, thus vaccine may have a role in controlling the spread of antibiotic resistance (10).

Vaccines are the cornerstone of prevention and control of bacterial meningitis. Vaccines for *N. meningitidis* made up of capsular polysaccharide have been available and used since the 1970s. These include a bivalent vaccine (serogroups A and C), a trivalent vaccine (A, C, Y), and a quadrivalent vaccine (A, C, W135, and Y). Timely mass-vaccination campaigns using polysaccharide vaccines can effectively interrupt the course of meningitis epidemics, but they are less effective in young children, do not provide long duration of protection, do not have sustained impact on nasopharyngeal carriage, and therefore do not interrupt person to person transmission. For this reason, they do not result in "herd immunity", which is the extension of protection to unvaccinated people in the community.

In 2010, a new serogroup A meningococcal conjugate vaccine was licensed, pre-qualified by WHO, and introduced in Burkina Faso, Mali, and Niger (11). Conjugate vaccines generally result in higher levels of protection, longer duration of protection, protection of children less than 2 years of age, and may interrupt nasopharyngeal carriage and transmission, resulting in herd immunity. When implemented in national preventive vaccination programs across the meningitis belt, it is hoped that the vaccine will prevent the occurrence of serogroup A epidemics. Traditional public health and bacteriologic surveillance, as well as molecular epidemiology, will play a crucial role in evaluating both the short- and long-term impact of these vaccination programs. For example, the need for vaccines to other serogroups, the potential re-emergence of serogroup A due to waning vaccine-induced immunity, or the emergence of new serogroups will only become evident through ongoing, high-quality surveillance.

Polysaccharide-protein conjugate vaccines for Hib are available for young children. In most industrialized countries, these vaccines have dramatically decreased the burden of Hib meningitis and virtually eliminated it as a public health problem through direct effects and induction of herd immunity without significant strain replacement. More recently, many developing countries have introduced, or plan to introduce, Hib vaccines through various global initiatives, such as the Hib Initiative and the GAVI Alliance, whose goals are to accelerate introduction of Hib vaccines in low and middle income countries.

A 23-valent polysaccharide vaccine is available for *S. pneumoniae*. Like other polysaccharide vaccines, it is not effective in children younger than two years of age; the group with the highest risk of *S. pneumoniae* meningitis. Newer polysaccharide-protein conjugate vaccines have been introduced in many industrialized countries, leading to dramatic declines in pneumococcal meningitis in infants and young children and in adults through induction of herd immunity (9). Currently, 7-valent, 10-valent, and 13-valent pneumococcal conjugate vaccines have been developed and have received WHO prequalification. In some settings, serotypes not covered by the 7-valent conjugate vaccine have increased somewhat following 7-valent conjugate vaccine introduction (25). As with Hib vaccine, global initiatives such as PneumoADIP and the GAVI Alliance have helped to accelerate introduction of these vaccines in low and middle income countries. As of the end of 2010, 42 countries were using a pneumococcal conjugate vaccine for routine infant immunization, including 3 low-income countries, and as many as 15 more low-income countries are slated to introduce vaccine in 2011 (26).

Role of the laboratory

Microbiologists play a critical role in gathering data both for clinical and public health decision making. Efficient and accurate microbiologic diagnosis of bacterial meningitis guides the choice of antibiotics and other treatment options for the patient. Collectively, serogroup or serotype results from isolates of bacterial meningitis in an effected population guide response efforts and determine the appropriate vaccine to be used. Similarly, microbiologic surveillance is critical to guide appropriate antibiotic therapy through the identification of local resistance profiles. Thus, the role of the microbiology laboratory is essential to preventing morbidity and mortality from bacterial meningitis.

Infection with *N. meningitidis* may be acquired through working with bacterial isolates in the microbiology laboratory if appropriate protective procedures are not followed (19). Microbiologists who routinely work with these isolates are at increased risk for infection. This risk highlights the importance of consistent adherence to biosafety procedures. In addition, vaccination against meningococcal disease is recommended for microbiologists who routinely work with *N. meningitidis*, and antimicrobial chemoprophylaxis should be used if lapses in biosafety procedures result in exposure to the organism.

Recommended reading

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